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Obesity attenuates serum 25-hydroxyvitamin D response to cholecalciferol therapy in critically ill patients

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ABSTRACT

Objectives: The presence of obesity may confound cholecalciferol dosing in vitamin D–deficient patients owing to potentially decreased bioavailability. The aim of this retrospective study was to evaluate cholecalciferol therapy in vitamin D-deficient, critically ill trauma patients with and without obesity.
Methods: Adult patients with severe traumatic injuries who had a serum 25-hydroxyvitamin D (25-OH vit D) <50 nmol/L were prescribed 10 000 IU of liquid cholecalciferol daily. Efficacy was defined as achievement of a 25-OH vit D of 75 to 200 nmol/L. Safety was evaluated by the presence of hypercalcemia (serum ionized calcium >1.32 mmol/L). Fifty-three patients (18 obese, 35 non-obese) were identified for study.
Results: Despite similar baseline concentrations (36 ± 7 versus 37 ± 7 nmol/L; P = NS), 25-OH vit D response was attenuated for those with obesity after 1 and 2 wk of cholecalciferol therapy (51 ± 18 versus 66 ± 27 nmol/L, $P < 0.01$; 68 ± 19 versus 92 ± 25 nmol/L, $P < 0.01$, respectively). Patients with obesity also tended to experience less hypercalcemia (22% versus 49% of patients, respectively) post-cholecalciferol therapy.
Conclusion: Obesity alters the response to cholecalciferol therapy in critically ill patients with severe traumatic injuries.

Introduction

A growing body of evidence indicates that vitamin D deficiency is prevalent among the critically ill [1–4]. Vitamin D deficiency in critically ill patients has been associated with worsened clinical outcomes, including increased risk for infectious complications, lengthened hospital stay, and worsened mortality [1–12]. Three-fourths of critically ill patients with traumatic injuries admitted to the intensive care unit (ICU) at our institution exhibit a serum 25-hydroxyvitamin D concentration (25-OH vit D) <50 nmol/L (20 ng/mL) [3], are highly catabolic [13,14], have a prolonged ICU length of stay (LOS) [13–15], and are susceptible to infections and surgical complications [13–15]. Preliminary evidence suggests cholecalciferol supplementation in critically ill patients with severe vitamin D deficiency or in vitamin D-deficient patients with a prolonged ICU LOS reduces hospital mortality [16,17]. Thus, these patient populations may represent subpopulations of critically ill patients whereby identification of vitamin D deficiency and its subsequent treatment could be of potential clinical relevance. However, defining the most appropriate dosage, particularly in obese patients, can be problematic. Obesity presents as a pharmacologic challenge because individuals with obesity have demonstrated decreased bioavailability when given daily maintenance doses of vitamin D [18,19]. The effects of obesity on vitamin D response to daily cholecalciferol therapy in critically ill patients has not been evaluated. Because obesity is prevalent in ~30% of ICU patients in the United States [14,20], evaluation of cholecalciferol dosing is warranted. The purpose of this study was to assess the influence of obesity on the efficacy and safety of a fixed cholecalciferol dosage in critically ill trauma patients with a serum 25-OH vit D concentration <50 nmol/L (20 ng/mL).

Materials and methods

Study population and design

Adult patients (>17 y of age), admitted to the trauma ICU of the Presley Memorial Trauma Center in Memphis, TN, and referred to the Nutrition Support

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Service (NSS) for enteral nutrition (EN), who also received daily cholecalciferol therapy were retrospectively evaluated for study inclusion. Patients with a serum 25-OH vit D concentration <50 nmol/L (20 ng/mL) were prescribed 10 000 IU/d of liquid cholecalciferol via the feeding tube as part of the routine practice of the NSS. Patients were excluded from evaluation if less than two serial weekly serum 25-OH vit D measurements were done or if the patients required hemodialysis or renal replacement therapy; had a past medical history of cancer with bone metastases; had a history of bone disease with receipt of vitamin D, calcium, or bisphosphonate therapy; had chronic granuloma-forming disorders such as tuberculosis or sarcoidosis; could not receive EN or oral medications; or had received parenteral nutrition (PN) for ≥10 d. Pregnant women also were excluded.

Study candidates were identified from the NSS monitoring records. The patient's electronic medical record and NSS monitoring record were retrospectively reviewed for data retrieval. The study was approved and conducted in accordance with the guidelines established by the University of Tennessee Health Science Center Institutional Review Board and Regional One Health Office of Medical Research. The need for written informed consent was waived.

Nutritional management

Patients were preferentially given EN by a naso- or orogastric tube. An estimated preresuscitation body weight was used to determine target nutrition goals whenever possible. Patients were categorized as having obesity as evidenced by a body mass index (BMI) of ≥30 kg/m^2 [21]. Target daily caloric and protein intakes for the non-obese patients were 25 to 32 kcal/kg and 2 to 2.5 g/kg, respectively [13]. Caloric and protein intakes for patients with obesity were dosed based on calculated ideal body weight [22] with an intended daily caloric and protein goal of ≤25 and 2 to 2.5 g/kg, respectively [21]. If the patient's estimated injury severity score [23] was >20, an enteral formula containing glutamine, arginine, and fish oil (1.3 kcal/mL, 78 g protein/L) was initiated [15]. Otherwise, patients received a conventional polymeric (1 kcal/mL, 62 g protein/L), high-protein (1 kcal/mL, 93 g protein/L), or diabetic (1.2 kcal/mL, 60 g protein/L) formula. Liquid protein supplements were also given. The feeding was advanced over 2 to 3 d to achieve the target regimen. Blood glucose concentrations were maintained between 70 and 150 mg/dL with insulin therapy when necessary [24,25].

Measured variables

An initial serum 25-OH vit D determination was performed within the first several days after admission to the ICU and after fluid resuscitation in an effort to avoid erroneously depressed serum 25-OH vit D concentrations [26]. Subsequent serial serum 25-OH vit D determinations were obtained weekly in conjunction with other laboratories (e.g., prealbumin, C-reactive protein, triacylglycerols, etc.) as ordered by the NSS as part of the patient's routine clinical care. Subsequent sequential serum 25-OH vit D measurements were only done while the patient received cholecalciferol during the patient's ICU stay. Serum ionized calcium concentrations (iCa) were also performed at least weekly but often done more frequently as warranted by patient condition with the presence and treatment of calcium abnormalities and follow-up evaluation [27,28].

Measurement of serum 25-OH vit D was conducted by the hospital laboratory via an automated chemiluminescent microparticle immunoassay (Architect System, Abbott Laboratories, Abbott Park, IL, USA). Intra- and interassay coefficients of variance were between 1.4% and 4.6% for concentrations ranging from 45 to 195 nmol/L (18–78 ng/mL). The minimal detection limit was 20 nmol/L (8 ng/mL). Verification studies for accurate concentration determination ranged from 32 to 240 nmol/L (13–96 ng/mL) per the manufacturer's recommendation [29]. Minimum concentrations were reported as <32 nmol/L (13 ng/mL) by the hospital laboratory and recorded as 32 nmol/L (13 ng/mL) for this study.

Cholecalciferol therapy

Patients with vitamin D deficiency, defined as a serum 25-OH vit D <50 nmol/L (20 ng/mL) [30], were given 10 000 IU/d of the liquid form of cholecalciferol (400 units/mL) per the feeding tube. Cholecalciferol therapy was discontinued when a serum 25-OH vit D concentration >75 nmol/L (30 ng/mL) was achieved, the patient was discharged from the ICU, EN was discontinued and an oral diet initiated, the iCa was >1.32 mmol/L, or when the NSS signed off the patient case. Efficacy of cholecalciferol therapy was defined as achievement of a serum 25-OH vit D of 75 to 200 nmol/L (30–80 ng/mL). Safety of cholecalciferol therapy was evaluated by the presence of hypercalcemia (iCa >1.32 mmol/L), severe hypercalcemia (iCa >1.49 mmol/L), or hypervitaminosis D (serum 25-OH vit D concentration >200 nmol/L [80 ng/mL]).

Statistical analysis

Data analysis was conducted using SigmaPlot for Windows, version 11.2 (Systat Software, Point Richmond, VA, USA). The significance testing and reported probability values (P) were two-sided for all variables. $P < 0.05$ was established as statistically significant. Continuous data were expressed as mean ± SD. Data were evaluated for normality of the distribution by the Shapiro–Wilk test. Differences between groups were assessed using the Student's t test or Mann–Whitney U test depending on the distribution of the data. Nominal data were analyzed using χ^2 or Fisher exact test. Two-way analysis of variance with post hoc, pair-wise comparisons by the Student–Newman–Keuls method was used for comparing serial serum 25-OH vit D concentrations between groups over time.

Table 1
Patient demographic characteristics and serum laboratories

Variable	Obese (BMI >30 kg/m^2)	Non-Obese (BMI <30 kg/m^2)	P-value
N	18	35	
Male/Female	12/6	24/11	0.865
Race			
Black, n	8	15	0.994
White, n	9	18	
Hispanic/other, n	1	2	
Age, y	44 ± 15	41 ± 14	0.433
Admission diagnosis			
MVC, n	12	27	0.690
GSW/KSW, n	3	3	
Fall/Assault/Other, n	3	5	
ISS	30 ± 6	29 ± 10	0.776
Traumatic brain injury, n (%)	9 (50)	22 (63)	0.545
BMI, kg/m^2	37.4 ± 7	24.3 ± 2.9	0.001
Height, cm	173 ± 10	176 ± 9	0.181
Weight, kg	111 ± 17	76 ± 11	0.001
EtOH history, n (%)	5 (28)	6 (17)	0.478
Initial serum iCa, mmol/L	1.17 ± 0.05	1.19 ± 0.06	0.350
Initial WBC, cells/mm^3	17.5 ± 5.2	17.6 ± 8.9	0.599
Initial T_{max}°C	38.4 ± 0.7	37.7 ± 1.2	0.024
Serum C-reactive protein, mg/dL	26.8 ± 4.1	22.3 ± 11.3	0.240
Serum prealbumin, mg/L	71 ± 36	82 ± 42	0.293
Serum albumin, g/L	24 ± 2	24 ± 3	0.517

BMI, body mass index; EN, enteral nutrition; EtOH, ethanol abuse; GSW, gunshot wound; iCa, ionized calcium concentration; ISS, injury severity score; KSW, knife stab wound; MVC, motor vehicle crash; n, number of patients; PN, parenteral nutrition; T_{max}, maximum temperature; WBC, white blood cell count.

Results

Patient characteristics

Fifty-three patients (18 obese, 35 non-obese) were identified for study. Most patients were male (68%), caucasian (51%), admitted to the hospital owing to a motor vehicle collision (75%), and survived (92%). Nearly all patients were ventilator dependent (98%) and had an Injury Severity Score reflective of severe injury (Table 1). More than 50% of the patients experienced traumatic brain injury. Patients had an elevated white blood cell count, markedly elevated serum C-reactive protein concentration, and depressed serum albumin concentration (Table 1). Serum albumin concentrations were similar between groups after 1 and 2 wk of cholecalciferol therapy (27 ± 6 g/L versus 29 ± 4 g/L, $P = 0.065$ and 29 ± 5 g/L versus 29 ± 4 g/L, $P = 0.767$) for the obese and non-obese patients, respectively. EN was begun 3 ± 2 d after admission to the ICU for both obese and non-obese groups, respectively ($P = 0.640$). More patients with obesity required supplemental PN than the non-obese owing to enteral feeding intolerance issues (28% versus 6%, respectively; $P = 0.03$). Outside of body weight and BMI, there were no clinically appreciable differences in patient characteristics between the obese and non-obese groups. Details regarding patient characteristics for the obese and non-obese patient groups are given in Table 1.

Effect of obesity on cholecalciferol efficacy and safety

Baseline serum 25-OH vit D concentrations were obtained on hospital day 4 ± 2 and 5 ± 5 for the obese and non-obese groups, respectively ($P = 0.782$). Despite a similar baseline serum 25-OH vit D concentration between the obese and non-obese groups (36 ± 7 nmol/L or 14.5 ± 2.9 versus 37 ± 7 nmol/L or 14.9 ± 2.8 ng/mL, $P = 0.429$), patients with obesity experienced an attenuated rise in serum 25-OH vit D concentration compared with non-obese patients at 1 and 2 wk after initiation of cholecalciferol therapy ($P < 0.001$; Fig. 1). Serum 25-OH vit D concentrations were 25% ± 4% and 32% ± 6% lower for the obese patients than for the non-obese at 1 and 2 wk, respectively. This difference in responsiveness was not attributable to differences in the total number of doses received during the observation period (10 ± 3 versus 9 ± 2 doses, respectively, $P = 0.391$). More non-obese patients tended to achieve a normal serum 25-OH vit D concentration than those with obesity after 1 and 2 wk of cholecalciferol therapy (Table 2). None of the patients experienced hypervitaminosis D. Patients with obesity tended to experience less mild hypercalcemia and severe hypercalcemia than those without obesity; however, these trends did not achieve statistical significance (Table 2). The maximum serum iCa concentration occurred on hospital days 18 ± 8 and 16 ± 6 for those with and without obesity, respectively ($P = 0.317$). Clinical outcomes including survival, sepsis, ventilator days, ICU LOS, and hospital LOS were similar between groups (Table 3).

Table 2
Cholecalciferol safety and efficacy

Variable	Obese (BMI >30 kg/m^2)	Non-obese (BMI <30 kg/m^2)	*P*-value
N	18	35	
Hospital day cholecalciferol started, d	6 ± 2	7 ± 5	0.864
Cholecalciferol therapy duration, d	15 ± 5	12 ± 5	0.046
Achieved 25-OH vit D >29.9 ng/mL at 1 wk, n (%)	1 (6)	9 (26)	0.137
Achieved 25-OH vit D >29.9 ng/mL at 2 wk, n (%)	5 (28)	20 (57)	0.082
iCa >1.32 mmol/L, n (%)	4 (22)	17 (49)	0.119
iCa >1.49 mmol/L, n (%)	0 (0)	2 (4)	0.543

25-OH vit D, serum 25-hydroxyvitamin D concentration; BMI, body mass index; iCa, serum ionized calcium concentration.

Discussion

Vitamin D deficiency, as defined by a serum 25-OH vit D concentration <50 nmol/L (20 ng/mL), occurred in 76% of 158 critically ill patients with severe traumatic injuries who required a prolonged ICU stay and specialized nutrition support therapy [3]. This observation was important because serum 25-OH vit D concentrations <50 nmol/L (20 ng/mL) in critically ill patients has been associated with an increased rate of infectious complications, longer hospital LOS, and worsened mortality [1–3,5–12]. The plausibility of vitamin D deficiency being associated with poorer outcomes in critically ill patients relates to recent discoveries of

Table 3
Clinical outcomes

Variable	Obese (BMI >30 kg/m^2)	Non-obese (BMI <30 kg/m^2)	*P*-value
N	18	35	
Survived, n (%)	16 (89)	33 (94)	0.598
Sepsis, n (%)	10 (56)	21 (60)	0.987
Ventilator days	18 ± 14	17 ± 9	0.590
ICU LOS, d	23 ± 12	21 ± 9	0.895
Hospital LOS, d	39 ± 20	35 ± 16	0.645

BMI, body mass index; ICU, intensive care unit; LOS, length of stay.

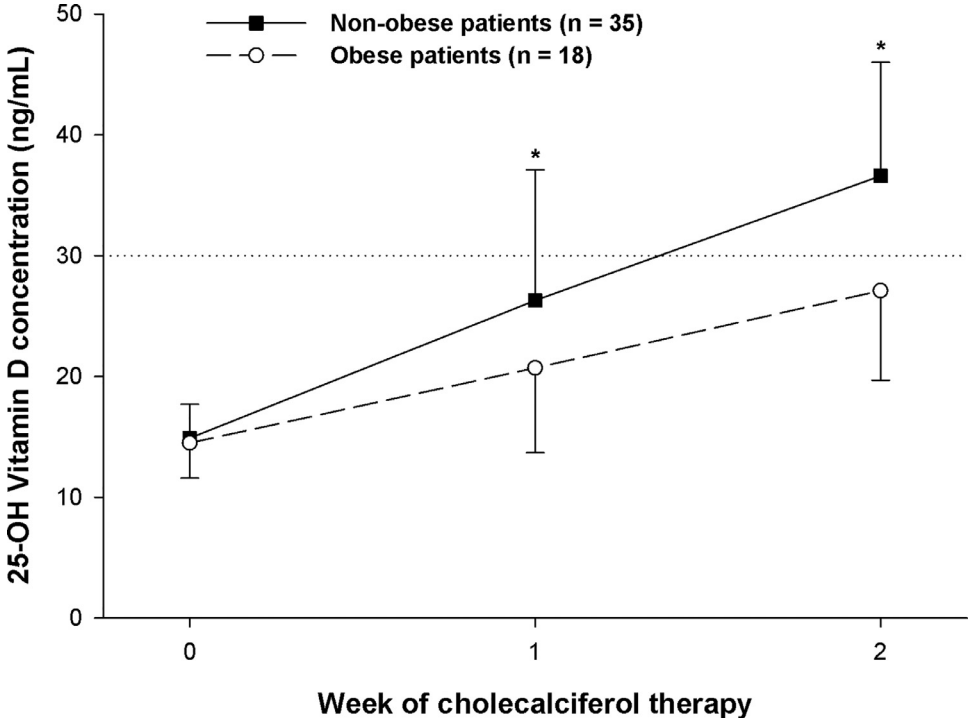

Fig 1. Impact of obesity on serial serum 25-hydroxyvitamin D concentrations during cholecalciferol therapy ($P < 0.001$). To convert ng/mL to nmol/L, divide by the concentration in ng/mL by 0.4. *$P < 0.01$ between groups.

vitamin D's multiple pleotropic effects beyond calcium homeostasis, bone health, and muscle function [31,32]. These discoveries indicated that synthesis of 1,25 di-hydroxyvitamin D within immune cells, derived from circulating 25-OH vit D, modulates the innate immune and adaptive response at the integumentary barrier sites to infectious pathogens by triggering production of cathelicidin and other antimicrobial peptides [33–35]. Because epithelial barrier site infections, such as ventilator-associated pneumonia, are common complications leading to death in ~20% of critically ill patients with severe traumatic injuries [36], treatment of vitamin D deficiency in these patients may be a plausible therapeutic intervention.

Obesity is a significant risk factor associated with the development of vitamin D deficiency and appears independent of age, latitude, exposure to sunlight, or a consistent dosage exposure to ultraviolet irradiation [3,12,19,37–41]. There are numerous potential etiologies for the development of a lower serum 25-OH vit D concentration in individuals with obesity [12,40]. One mechanism is the simple sequestration of this fat-soluble vitamin into the patients' abundant adipose tissues. However, this proposed mechanism is complicated by an imperfect inverse linear relationship between serum vitamin D concentration and body weight. Thus, a volumetric or dilutional model rather than sequestration may better explain the depressed concentrations observed in obese patients [41]. Overall, these potential compartmentally related body mechanisms likely oversimplify the role of obesity in depressing serum 25-OH vit D concentrations because adipokines, such as leptin and adiponectin, may also alter vitamin D homeostasis [42].

Despite the propensity for patients with obesity to exhibit a lower serum 25-OH vit D concentration than non-obese individuals, there was no difference in baseline serum 25-OH vit D concentrations before cholecalciferol therapy between critically ill obese and non-obese patients in the present study (Fig. 1). This observation of equivalent low serum concentrations of 25-OH vit D between the two groups may be a signal of an activated immune system owing to stress-related hormone and cytokine production, which in turn causes a reprioritization of hepatic protein synthesis [43], resulting in a decreased production of albumin and vitamin D–binding protein [44]. In addition, augmented cytokine and counter-regulatory hormone production during critical illness may result in a worsened ability to prevent renal vitamin D excretion [45], increased interstitial extravasation via increased vascular permeability [44], upregulation of the calcium-sensing receptor of the parathyroid gland causing a decrease in parathyroid hormone production [46], and increased consumption of vitamin D [35]. Evidence for a comparable activated immune system between patient groups was reflected by similarity in high injury severity scores, prevalence of patients with traumatic brain injury and sepsis, an elevated C-reactive protein concentration, an elevated white blood cell count, depressed serum prealbumin and albumin concentrations, and prolonged ICU and hospital LOS (Tables 1 and 3). The observed low baseline concentrations in the present study were not likely attributable to factitious hypovitaminosis D owing to fluid resuscitation [26] because mean baseline observations were conducted 4 to 5 d after ICU admission with no patients having an observation sooner than 2 d after admission to the ICU. Taken together, these data indicate that high patient acuity associated with severe traumatic injuries most likely explained similar baseline serum concentrations between the obese and non-obese patient groups.

Obesity may be a complicating factor in the development of an appropriate therapeutic dosage regimen that served as the premise for its evaluation in this study. Three-year administration of 4000 IU/d of cholecalciferol has been demonstrated to be safe with minimal hypercalcemia (6% versus 3% for placebo) and efficacious for achieving and maintaining plateau 25-OH vit D concentrations near 100 nmol/L (40 ng/mL) in patients with advanced cardiac disease and a median BMI of 28 kg/m^2 [47]. A fixed cholecalciferol dosage of 10 000 IU/d was selected because it represents the recommended daily upper limit by the European Endocrine Society [30] and because our intent was for short-term use while the patient was in the ICU. This dosage was considered safe by the European Endocrine Society because it did not cause hypercalcemia, hypercalciuria, or serum 25-OH vit D concentrations >200 nmol/L (80 ng/mL) after 5 mo of therapy in healthy adults [18,30,48]. Our data indicated that critically ill patients with obesity had a significantly attenuated response to cholecalciferol therapy with lower 25-OH vit D concentrations after 1 and 2 wk of therapy than those critically ill patients without obesity (Fig. 1). Less than one-third of patients with obesity compared with two-thirds of non-obese patients had achieved a serum 25-OH vit D concentration of 70 to 200 nmol/L (30–80 ng/mL) by the second week of cholecalciferol therapy (Table 2).

The present findings that patients with obesity exhibit an attenuated response to cholecalciferol therapy concurs with others' findings [18,19]. However, our study population differed from these other studies that examined the effect of obesity in that we examined serum 25-OH vit D response to cholecalciferol therapy under the conditions of critical illness with severe traumatic injuries as opposed to healthy, ambulatory obese and non-obese subjects [18,19]. A 30% difference in body weight (111 versus 76 kg) between the obese and non-obese groups implied that the observed decreased 25-OH vit D concentration for the obese patients may have been due to volumetric dilution [41] and fat sequestration [19] as the principal volume of distribution determinants in the pharmacokinetic interpretation of these data. However, adipokine-mediated alterations in vitamin D retention or elimination as a contributing factor for the impaired response to supplementation by those with obesity cannot be excluded.

To evaluate the safety of cholecalciferol therapy, we evaluated patients for the presence of hypervitaminosis D or hypercalcemia. None of the patients experienced a 25-OH vit D serum concentration >200 nmol/L (80 ng/mL), indicating avoidance of hypervitaminosis D. Serum iCa concentrations tended to parallel the observed pharmacokinetic response in that patients with obesity tended to experience less hypercalcemia than the non-obese group (22% versus 49%, respectively; Table 2). None of the patients with obesity had an episode of severe hypercalcemia (>1.49 mmol/L) during the observation period in contrast to 4% of the non-obese. Although it may be argued that development of mild hypercalcemia is clinically irrelevant, the appearance of hypercalcemia without hypervitaminosis D is concerning and conflicts with the safety recommendations in current guidelines for the treatment of vitamin D deficiency [30]. Our previous observation of calcium abnormalities in critically ill patients with traumatic injuries, conducted before routine administration of cholecalciferol for patients with a serum 25-OH vit D concentration <50 nmol/L (20 ng/mL), demonstrated only a 6% incidence of mild hypercalcemia within the first week after ICU admission [49]. Our previous investigation with differing doses of ergocalciferol indicated a 6%, 11%, and 26% incidence of hypercalcemia [50]. This is in contrast to nearly 40% of patients given cholecalciferol by the second or third week post-ICU admission in this study. It is unclear why this adverse phenomenon occurred, but saturation of vitamin D–binding protein and albumin may have occurred (attributable to their decreased concentrations during critical illness), which resulted in excessive 1,25 dihydroxyvitamin D production [51]. Alternatively, the hypercalcemia may have been attributed to prolonged immobility or critical illness–associated metabolic bone disease [52]. Further evaluation of this phenomenon is warranted.

This study had limitations beyond its retrospective, single-center design. There is controversy regarding what threshold concentration best defines vitamin D deficiency. We used the European Endocrine Society guidelines of a serum 25-OH vit D concentration of <50 nmol/L (20 ng/mL) [30], whereas the Institute of Medicine recommends a threshold serum concentration of <30 nmol/L (12 ng/mL) [53]. The chemiluminescent microparticle immunoassay for 25-OH vit D lacks precision at low serum concentrations. Lack of determination of serum concentrations of vitamin D-binding protein, free 25-OH vit D, 1,25-dihydroxyvitamin D, and parathyroid hormone concentrations could have provided further insight regarding whether normal or elevated free vitamin D concentrations were achieved (despite a low or normal total serum concentration) and potentially may have provided an explanation for those patients who experienced hypercalcemia. In addition, steady-state serum 25-OH vit D concentrations were unlikely achieved owing to daily variability in clinical status of the patients, a short-term (2-wk) evaluation period, and a small number of dosage omissions owing to enteral feeding intolerance or a surgical procedure. The study sample size for the obese and non-obese groups was limited. Finally, use of a standard dose, without adjustment for body weight, may have contributed to the differences in the pharmacokinetic and pharmacodynamic profiles between the groups.

Conclusions

Critically ill patients with severe traumatic injuries and obesity exhibited an attenuated serum 25-OH vit D response to a standardized dose of cholecalciferol compared with those without obesity. Patients with obesity also tended to experience less hypercalcemia than non-obese patients during cholecalciferol therapy. The presence of obesity alters the response to cholecalciferol therapy in critically ill patients with severe traumatic injuries.

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References

[1] Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, et al. Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Crit Care Med 2011;39:671–7.
[2] Braun AB, Gibbons FK, Litonjua AA, Giovannucci E, Christopher KB. Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. Crit Care Med 2012;40:63–72.
[3] Dickerson RN, Van Cleve JR, Swanson JM, Maish 3 GO, Minard G, Croce MA, et al. Vitamin D deficiency in critically ill patients with traumatic injuries. Burns Trauma 2016;4:28.
[4] Borgermann J, Lazouski K, Kuhn J, Dreier J, Schmidt M, Gilis-Januszewski T, et al. 1,25-Dihydroxyvitamin D fluctuations in cardiac surgery are related to age and clinical outcome. Crit Care Med 2012;40:2073–81.
[5] Amrein K, Zajic P Schnedl C, Waltensdorfer A, Fruhwald S, Holl A, et al. Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Crit Care 2014;18:R47.
[6] Braun AB, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. Crit Care Med 2012;40:3170–9.
[7] Moromizato T, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. Crit Care Med 2014;42:97–107.
[8] Quraishi SA, Bittner EA, Blum L, McCarthy CM, Bhan I, Camargo Jr. CA. Prospective study of vitamin D status at initiation of care in critically ill surgical patients and risk of 90-day mortality. Crit Care Med 2014;42:1365–71.
[9] Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G. Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crit Care 2011;15:R292.
[10] Blay B, Thomas S, Coffey R, Jones LM, Murphy C. Evaluation of vitamin D status in burn injured patients. J Burn Care Res 2016;37:S209.
[11] Higgins DM, Wischmeyer PE, Queensland KM, Sillau SH, Sufit AJ, Heyland DK. Relationship of vitamin D deficiency to clinical outcomes in critically ill patients. JPEN J Parenter Enteral Nutr 2012;36:713–20.
[12] Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev 2015;16:341–9.
[13] Dickerson RN, Pitts SL, Maish 3rd GO, et al. A reappraisal of nitrogen requirements for patients with critical illness and trauma. J Trauma Acute Care Surg 2012;73:549–57.
[14] Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition 2002;18:241–6.
[15] Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE, et al. A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. Ann Surg 1996;224:531–43.
[16] Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA 2014;312:1520–30.
[17] Martucci G, Tuzzolino F, Arcadipane A, Pieber TR, Schnedl C, Urbanic Purkart T, et al. The effect of high-dose cholecalciferol on bioavailable vitamin D levels in critically ill patients: a post hoc analysis of the VITdAL-ICU trial. Inten Care Med 2017;43:1732–4.
[18] Drincic A, Fuller E, Heaney RP, Armas LA. 25-Hydroxyvitamin D response to graded vitamin D(3) supplementation among obese adults. J Clin Endo Metab 2013;98:4845–51.
[19] Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.
[20] Dickerson RN, Medling TL, Smith AC, Maish 3rd GO, Croce MA, Minard G, et al. Hypocaloric, high-protein nutrition therapy in older vs younger critically ill patients with obesity. JPEN J Parenter Enteral Nutr 2013;37:342–51.
[21] Choban P, Dickerson R, Malone A, Worthington P, Compher C. the American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: nutrition support of hospitalized adult patients with obesity. JPEN J Parent Enteral Nutr 2013;37:714–44.
[22] Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm 1974;8:650–5.
[23] Baker SP, O'Neill B, Haddon Jr W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187–96.
[24] Dickerson RN, Swiggart CE, Morgan LM, Maish 3rd GO, Croce MA, Minard G, et al. Safety and efficacy of a graduated intravenous insulin infusion protocol in critically ill trauma patients receiving specialized nutritional support. Nutrition 2008;24:536–45.
[25] Cogle SV, Smith SE, Maish 3rd GO, Minard G, Croce MA, Dickerson RN. Sliding scale regular human insulin for identifying critically ill trauma patients who require intensive insulin therapy and for glycemic control in those with mild to moderate hyperglycemia. J Pharm Nutr Sci 2017;7:106–15.
[26] Krishnan A, Ochola J, Mundy J, Jones M, Kruger P, Duncan E, et al. Acute fluid shifts influence the assessment of serum vitamin D status in critically ill patients. Crit Care 2010;14:R216.
[27] Dickerson RN, Morgan LG, Cauthen AD, Alexander KH, Croce MA, Minard G, et al. Treatment of acute hypocalcemia in critically ill multiple-trauma patients. JPEN J Parenter Enteral Nutr 2005;29:436–41.
[28] Dickerson RN, Morgan LM, Croce MA, Minard G, Brown RO. Treatment of moderate to severe acute hypocalcemia in critically ill trauma patients. JPEN J Parenter Enteral Nutr 2007;31:228–33.
[29] 25-OH vitamin D Architect System package insert. Abbott Park, IL: Abbott Laboratories; 2011.
[30] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endo Metab 2011;96:1911–30.
[31] Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue Int 2013;92:151–62.
[32] Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. Osteoporos Int 2002;13:187–94.
[33] Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Molec Nutr Food Res 2011;55:96–108.
[34] Han JE, Ziegler TR. Vitamin D supplementation in sepsis and critical illness: where are we now? Am J Resp Crit Care Med 2014;190:483–5.
[35] Kempker JA, Tangpricha V, Ziegler TR, Martin GS. Vitamin D in sepsis: from basic science to clinical impact. Crit Care 2012;16:316.
[36] Magnotti LJ, Croce MA, Fabian TC. Is ventilator-associated pneumonia in trauma patients an epiphenomenon or a cause of death? Surg Infect 2004;5:237–42.
[37] Andreozzi P, Verrusio W, Viscogliosi G, Summa ML, Gueli N, Cacciafesta M, et al. Relationship between vitamin D and body fat distribution evaluated by DXA in postmenopausal women. Nutrition 2016;32:687–92.
[38] Gangloff A, Bergeron J, Pelletier-Beaumont E, Nazare JA, Smith J, Borel AL, et al. Effect of adipose tissue volume loss on circulating 25-hydroxyvitamin D levels: results from a 1-year lifestyle intervention in viscerally obese men. Int J Obes 2015;39:1638–43.
[39] Shafinaz IS, Moy FM. Vitamin D level and its association with adiposity among multi-ethnic adults in Kuala Lumpur, Malaysia: a cross sectional study. BMC Public Health 2016;16:232.
[40] Vanlint S. Vitamin D and obesity. Nutrients 2013;5:949–56.
[41] Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity 2012;20:1444–8.

[42] Chirumbolo S. The role of vitamin D towards immune tolerance in white adipose tissue (WAT). Endocr Metab Immune Disord Drug Targets 2015;15:277–87.
[43] Sganga G, Siegel JH, Brown G, Coleman B, Eiles 3rd CE, Belzberg H, et al. Reprioritization of hepatic plasma protein release in trauma and sepsis. Arch Surg 1985;120:187–99.
[44] Czarnik T, Czarnik A, Gawda R, Piwoda M, Marszalski M, Maj M, et al. Vitamin D kinetics in the acute phase of critical illness: a prospective observational study. J Crit Care 2018;43:294–9.
[45] Ingels CM, Van Cromphaut SJ, Wouters PJ, Moller HJ, Van Herck E, Jans I, et al. Effect of restoration of 25 OHD3 status in prolonged critical illness on serum innate immunity parameters LL-37 and sCD163. Crit Care 2010;14:S198–9.
[46] Klein GL. The interaction between burn injury and vitamin D metabolism and consequences for the patient. Curr Clin Pharmacol 2008;3:204–10.
[47] Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. Eur Heart J 2017;38:2279–86.
[48] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[49] Dickerson RN, Alexander KH, Minard G, Croce MA, Brown RO. Accuracy of methods to estimate ionized and "corrected" serum calcium concentrations in critically ill multiple trauma patients receiving specialized nutrition support. JPEN J Parenter Enteral Nutr 2004;28:133–41.
[50] Dickerson RN, Berry SC, Ziebarth JD, Swanson JM, Maish III GO, Minard G, et al. Dose-response effect of ergocalciferol therapy on serum 25-hydroxyvitamin D concentration during critical illness. Nutrition 2015;31:1219–23.
[51] Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. J Nutr 2006;136:1117–22.
[52] Nierman DM, Mechanick JI. Bone hyperresorption is prevalent in chronically critically ill patients. Chest 1998;114:1122–8.
[53] Dietary reference intakes: Calcium and vitamin D. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. Dietary reference intakes: Calcium and vitamin D, Washington DC: National Academies Press; 2011.